

## LETTERS TO THE EDITOR

### Carbohydrate antigen 19-9 in cerebrospinal fluid and within malignant cells in a case of leptomeningeal carcinomatosis

Carcinoembryonic antigen (CEA) concentrations in CSF hold promise as an indicator of metastatic leptomeningeal involvement by carcinoma.<sup>1,2</sup> We describe a patient with leptomeningeal carcinomatosis showing a high concentration of carbohydrate antigen 19-9 (CA 19-9) but a normal CEA concentration in CSF despite equally positive immunostaining in the cytoplasm of tumour cells in CSF.

A 44 year old man was admitted complaining of headaches and diplopia over 3 months. Neurologically, the patient was alert despite neck stiffness. Multiple cranial nerve dysfunction was apparent, specifically bilateral lateral gaze palsy, inability to move his jaw due to masseter palsy, facial diplegia, left soft palate weakness, and absence of gag reflex on the left. Four limb ataxia was evident, and his gait was wide based and unsteady. Reflexes were symmetrically hypoactive in all extremities and pathological reflexes were absent.

Chest CT disclosed nodular, contrast enhancing, left upper lung densities. Gastric fibroscopy and abdominal CT were unrevealing. Non-contrast brain MRI was normal. On lumbar puncture, opening pressure was high (160 mm H<sub>2</sub>O). His CSF was xanthochromic and contained 9 cells/mm<sup>3</sup>, 117 mg/dl protein, and 48 mg/dl glucose. Cytological examination of CSF disclosed scattered large cells with irregularly shaped, polymorphic nuclei, sometimes with large cytoplasmic vacuoles characteristic of adenocarcinoma (fig 1 A, B). The CEA concentra-

tion (radioimmunoassay: Eiken, Tokyo, Japan) in CSF remained low (1.1 ng/ml), unlike that in serum (81.1 ng/ml (upper normal limit 2.5 ng/ml)). By contrast, the CSF concentration of CA 19-9 (enzyme immunoassay: Dainabot, Tokyo, Japan) was extremely high (61.4 U/ml), whereas that in serum remained nearly normal (39.4 U/ml (upper limit 37 U/ml)).

Weekly intrathecal methotrexate administration (10 mg) for 5 weeks failed to improve neurological deficits or lower CSF CA 19-9 concentrations (fig 2). Subsequently treatment was changed to weekly intrathecal cytarabine (30 mg) for 6 weeks, adding brainstem radiotherapy for the last 2 weeks. Headache and neck stiffness were relieved. The cranial nerve palsies and four limb ataxia remained unchanged.

Repeat CSF analysis disclosed the disappearance of identifiable tumour cells and a marked decrease in CSF CA 19-9 concentration, from 78.9 to 16.4 U/ml, whereas that of CEA in CSF remained at its previous low concentrations despite continuing high CEA in serum. Two weeks later, the patient became deaf and confused. Concentrations of CA 19-9 increased in the CSF, and the patient died 26 weeks after admission. Permission for postmortem examination was withheld.

Immunocytochemical studies of tumour cells in the CSF from the patient and two control patients with leptomeningeal carcinomatosis from squamous cell lung cancer in whom CEA concentrations in serum and CSF were normal or negative were performed as follows. Cells obtained from CSF at initial lumbar puncture were collected on slides using cytopsin equipment. Cell preparations were stained using monoclonal antibodies against CA 19-9 or CEA (Lipshaw, Detroit, MI, USA), both of which were labelled with peroxidase by the avidin-biotin complex method. For this staining, slides were fixed in acetone, air dried, and washed for 30 minutes in three changes of phosphate buffered saline (PBS). Additional PBS washes (15 minutes

in three changes) were interposed between the following steps. After the slides were incubated at 37°C for 20 minutes with monoclonal mouse primary antibody, they were incubated at 37°C for 20 minutes with biotinylated secondary antibody. After this the slides were placed for 10 minutes in PBS with 1.5% hydrogen peroxide and then incubated in avidin-biotin complex solution at 37°C for 20 minutes. After incubation for 5 minutes with diaminobenzidine (0.5 mg/ml) as substrate and hydrogen peroxide (0.3%) in PBS, the slides were counterstained with haematoxylin. The cytoplasm of the tumour cells was strongly positive for both CA 19-9 and CEA, indicating production of the markers by the cells (fig 1 C, D). Tumour cells in CSF from the two control patients with squamous lung cancer were immunocytochemically negative for CEA, arguing against false positive staining in the patient.

On the assumption that tumour markers with a molecular weight similar to that of IgG should have similar filtration transfer properties at the blood-CSF barrier, the portion of tumour marker (CA 19-9) produced was calculated in relation to IgG according to the equation<sup>1</sup>

$$\text{CA 19-9 loc} = \text{CA 19-9 CSF} - 0.7 \times \text{CSF/serum alb} \times 1000 \times \text{CA 19-9 serum}$$

$$1000$$

Ca 19-9 loc (U/ml) was 59.6 initially, 7.4 at 18 weeks later, and 57.5 at 26 weeks after admission.

CA 19-9 is a monoclonal antibody defined carbohydrate antigen<sup>1</sup> expressed by many carcinomas, which is useful for carcinoma

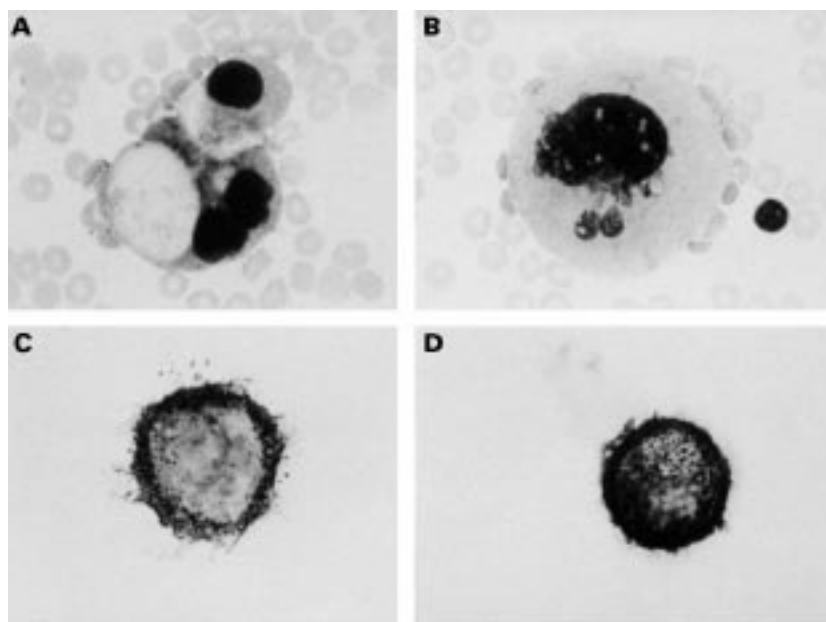


Figure 1 Tumour cells in CSF (A) three large cells surrounded by red cells contain hyperchromatic nuclei. A large cytoplasmic vacuole displaces the nucleus, suggesting a mucin producing adenocarcinoma (May-Giemsa×300). (B) An abnormally large cell (50 µ diameter) showing an irregularly shaped nucleus with inhomogeneous chromatin (May-Giemsa×300). (C) Immunocytochemical CA 19-9 staining in tumour cell cytoplasm (immunoperoxidase×300). (D) Cytoplasm of a tumour cell stained for CEA (immunoperoxidase×300).

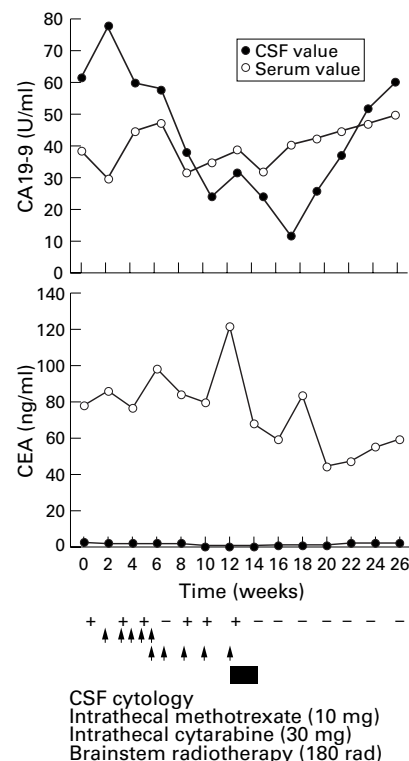


Figure 2 Clinical course and CSF and serum concentrations of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) in a patient with leptomeningeal carcinomatosis. After treatment with intrathecal cytarabine and brainstem radiotherapy, CSF CA 19-9 concentrations fell, but rose again after stopping treatment. Concentrations of CEA were consistently low in CSF and high in serum throughout the course.

detection, mainly in the digestive tract<sup>4</sup> but sometimes in lung adenocarcinoma.<sup>5</sup>

The present patient high CSF CA 19-9 concentration, in whom leptomeningeal carcinomatosis probably originated from lung carcinoma, raised two new issues. Firstly, this is the first report in which CSF concentrations of CA 19-9 but not those of CEA proved useful as a marker in leptomeningeal carcinomatosis. The case showed a high CSF/serum CA 19-9 ratio of 1.56 (61.4 U/ml/39.4 U/ml), indicating that the marker was produced and released by meningeal tumour cells. In addition to the evidence from calculations demonstrating local production of CA 19-9, tumour cells in CSF were shown to possess CA 19-9-producing ability by cytoplasmic immunostaining. Therefore, serial determinations of CA 19-9 concentration in CSF may be helpful in the diagnosis and clinical management of leptomeningeal carcinomatosis even when the CEA concentration in CSF is not increased.

The second point of interest is that the CEA concentration was not increased throughout the clinical course despite increases in serum, and despite CEA immunoreactivity in the cytoplasm of tumour cells in the CSF. This discrepancy indicates that CEA produced by tumour cells in the meninges was not effectively released into CSF, for unknown reasons. However, determination of both CEA and CA 19-9 concentrations in CSF may increase sensitivity and effectiveness of tumour markers in the diagnosis and monitoring of leptomeningeal carcinomatosis, as one may be raised in isolation.

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# Hereditary motor and sensory neuropathy type 1A associated with sensorineural deafness

The most common type of hereditary motor and sensory neuropathy type 1, HMSN 1A, is caused by a duplication of the gene for peripheral myelin protein 22 (PMP 22), situ-

ated on chromosome 17p. We report on a patient with this genotype with bilateral sensorineural deafness.

A 28 year old man presented with progressive distal weakness, numbness, and progressive bilateral hearing loss. He had first noticed problems with running in his early teens and at the age of 13 had two operations to correct bilateral pes cavus. His walking tolerance gradually deteriorated to half a mile unaided. At the age of 24, he had three operations to correct thoracic scoliosis and subsequently noticed progressive weakness of his hands. Since the age of 26 he had been aware of diminished sensation in his feet and progressive bilateral hearing loss. Medical history was unremarkable and he had not been exposed to any relevant drugs or toxins. There was no history of neurological problems among three siblings, his three children or the rest of his family. There was no parental consanguinity.

General medical examination disclosed bilateral pes cavus, palpable greater auricular nerves, and evidence of previous spinal surgery. Otoscopy was normal. Audiological examination showed bilateral sensorineural deafness (-40 dB at 6 kHz in both ears). Visual acuity, fundoscopy, and all other cranial nerves were normal. There was a typical essential tremor of both hands. In the limbs there was symmetric distal wasting, worse in the lower limbs, with corresponding weakness. Deep tendon reflexes were absent. Pinprick and vibration sensation were impaired in both feet.

Laboratory investigations showed no evidence of any underlying systemic disorder. Protein concentration in CSF was 1.55 g/l. Nerve conduction studies showed markedly diminished motor conduction velocities: right median nerve motor velocity was 16 m/s; right posterior tibial nerve motor velocity was 14m/s; sensory responses were unobtainable in the right sural and superficial peroneal nerves. Right sural nerve biopsy showed a severe demyelinating neuropathy with massive onion bulb formation. Genetic evaluation of a serum sample confirmed the presence of the PMP 22 duplication on chromosome 17. Brain stem auditory evoked responses (BAERs) were performed (table). Wave I latencies were significantly delayed compared with laboratory controls. Interwave I-V latencies were only marginally increased.

A recent paper on a series of 61 patients with the PMP 22 duplication reported no cases of deafness.<sup>1</sup> However, deafness and asymptomatic abnormalities of BAERs has been reported in association with HMSN. In one kindred, 61 patients had a history of hearing loss in association with an autosomal dominant HMSN type 1.<sup>2</sup> There were seven cases of sensorineural deafness among the 14 family members described by Cruse *et al*,<sup>3</sup> who had an autosomal dominant HMSN type 1. The four patients with symptomatic deafness described by Raglan *et al*<sup>4</sup> also con-

form to recognised criteria for a diagnosis of HMSN type 1 but more detailed clinical information on these patients is lacking. Perez *et al*<sup>5</sup> suggested, in a small community study, that the incidence of deafness in a mixed group of HMSN1 and HMSN 2 could be as high as 30%. Only the 77 year old female patient of Nicholson *et al*<sup>6</sup> is definitely HMSN 1A, and it could be speculated whether at this age deafness is a coincidental symptom.

Nicholson *et al*<sup>6</sup> have recently renewed interest in auditory abnormalities in patients with HMSN 1A. Our patient conforms to the pattern they found, with isolated delayed wave I latencies suggesting a problem in the distal VIIIth nerve, in which PMP 22 expression is known to occur. This is the first case report to provide incontrovertible evidence, with nerve biopsy and genetic analysis, of bilateral sensorineural deafness in a young patient with "a full house" phenotypically and genotypically for HMSN 1A.

Neurologists and otolaryngologists should be aware of this association, which may be commoner than previously thought.

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# Chronic inflammatory demyelinating polyneuropathy accompanied by carcinoma

We read the article by Antonie *et al* with interest.<sup>1</sup> We have also reported on a patient with chronic inflammatory demyelinating polyneuropathy (CIDP) accompanied by hepatocellular carcinoma who showed improvement after intravenous methylprednisolone injection.<sup>2</sup> On the basis of this experience, we investigated 20 consecutive patients with pathologically established hepatocellular carcinoma in our hospital and found another patient having definite CIDP using the criteria of the Ad Hoc subcommittee of the American Academy of Neurology.<sup>3</sup> This patient also had motor sensory neuropathy and showed improvement after intravenous methylprednisolone injection. Our two patients showed a motor sensory neuropathy affecting the four limbs. Their CSF contained high concentrations of protein and the study of conduction velocities and biopsied nerves showed demyelination.

Brain stem auditory evoked potentials in this patient show marked delay of wave I latencies with preservation of interwave I-V latencies compared with laboratory controls

Latency (ms)	Normal range Mean (SD)	HMSN 1A (n=1)	
		Left	Right
Wave I	1.7 (0.15)	2.22	2.37
Wave IV	5.1 (0.24)	6.30	6.33
Wave V	5.7 (0.25)	6.60	6.68
Interwave I-V	4.0 (0.23)	4.38	4.31

We did not find anti-GM1 antibodies in either patient. As discussed in Antonie *et al*<sup>1</sup> the association of carcinoma and primary demyelinating neuropathy has seldom been reported. However, the cases reported by Antonie *et al* as well as us suggest the possibility that weakness or clumsiness, which is sometimes seen in patients with carcinoma may be caused by CIDP, and these symptoms should not be misinterpreted as representing general weakness caused by malignancies. Further investigation with large numbers of patients may be useful in determining the mechanism.

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### Frequency, causes, and consequences of burns in patients with epilepsy

The increased incidence of burns in people with epilepsy has long been recognised. Previous surveys (via questionnaires in clinic or burns unit admissions) have identified cooking, showering, and heaters as the most common causes. The duration of epilepsy and frequency of seizures have been recognised as the greatest risk factors,<sup>1-4</sup> compounded by lack of awareness and education

among people with epilepsy about the risk of burns.<sup>3</sup>

The aim of this study was to determine the frequency, causes, and consequences of burns and scalds in patients with epilepsy. The population comprised patients with chronic epilepsy who were resident at the Chalfont Centre for Epilepsy (CCE). The residential part of the CCE consists of a series of houses that provide for varying degrees of independence in terms of self care. There is also a short stay tertiary referral inpatient assessment facility and a medical and nursing unit on site where any injury is documented and assessed.

The daily records of the Medical and Nursing Unit for the year June 1995-6 were examined and any record of a burn extracted and followed until it was recorded as healed. The records for the day of the burn were then examined to determine the cause of the burn and whether it was seizure related.

The residential houses were divided into three groups according to the level of self care of the patients within each. Dependency was largely governed by physical infirmity rather than by severity of the seizure disorder.

- Dependent (98 residents)—all meals and hot drinks provided and help given with personal care.
- Intermediate (94 residents)—all meals provided, some residents make their own hot drinks and there is a variable level of independence with personal care.
- Independent (111 residents)—independent with regard to hot drinks, personal care, and some meals.

The number of residents in each category were calculated at the end of the year and remained relatively constant during the 1 year period. Seizures occurring in all patients were recorded prospectively in seizure diaries.

The number of seizures in the same 1 year period (June 1995 - June 1996) were calculated from the case records of the 303 residents. The number of seizures in the 28 bed assessment unit could not be calculated for the year, as there was a high patient

turnover with a median stay of 32 days. The number of seizures from the residential houses were therefore extrapolated to allow for the number of patients in the assessment unit. No burns occurred in the assessment unit, which was classified as dependent with regard to the level of care made available to the inpatients.

A  $\chi^2$  test was applied to the number of burns occurring in houses of differing levels of dependence to examine the significance of observed variation. This was then repeated correcting for the median number of seizures per person, in the three groups.

The results are shown in the table. Whereas the frequency of burns is regarded as accurate, the number of seizures may be underreported as nocturnal or minor seizures may not have been seen and recorded. Information as to whether an injury was seizure related or not was unavailable in three, and the cause of the burn was unavailable in two cases. Of the severe burns, one required skin grafting with healing occurring over 3 months and one patient attended an accident and emergency department, but was not admitted, and the burn took 4 months to heal. Two of the severe burns were complicated by methicillin resistant *Staphylococcus aureus* (MRSA).

Infection, but healed uneventfully. Two other patients had burns that were also complicated by an infection but without growth of a particular organism. One received antibiotics and recovered quickly, the other was initially treated only with topical therapy and took longer to recover.

Most burns were related to seizures (19 of 34). This was particularly true of the more severe burns (five of six). A total of 18 631 seizures were recorded during the year meaning that about one seizure in every 980 resulted in a burn and one in every 3105 seizures resulted in a severe burn.

Most burns were caused by hot water injuries (25 of 34). More severe burns were mostly caused by larger quantities of water. Cookers, hot pipes, and heaters were rare causes of burns in this study.

There were significantly more burns in the more independent houses ( $p < 0.05$ ). The median number of seizures per person in the more independent houses was also greater as residents were placed in houses according to their physical disability rather than on the severity of their seizure disorder. Correcting for seizure frequency abolished the significance of the effect of level of dependence on the number of burns ( $p > 0.1$ ).

Burns are a serious but underrecognised complication of epilepsy. Previous studies have used two different approaches. The first has been to give patients attending an epilepsy clinic a questionnaire about any burns ever sustained.<sup>3,4</sup> This method relies on the memory of the patients involved and therefore biases recording towards serious injuries. These studies also gave little idea of frequency, as there was no time limit imposed. The second approach has been to consider patients with epilepsy admitted to burns units.<sup>1</sup> This again restricts the survey to severe burns. Neither method gives any idea of frequency as there is no set population with no calculation of the number of seizures over a period of time, hence no idea of level of risk.

The residents at the Chalfont Centre for Epilepsy live as normal a life as their level of disability allows. This means that some residents are not exposed to the same risk of burns as those living in the community. A

Factors influencing burns in patients with epilepsy

	Severity of burns (time to heal (days))				Total
	0-7	7-14	14-21	>21	
Burns (n)	17	8	3	6	34
Relation to seizure:					
Seizure	8	3	3	5	19
No seizure	8	4	0	0	12
Not known	1	1	0	1	3
Cause of burn:					
Kettle	2	1	1	2	6
Teapot	1	1	0	2	4
Cup	10	3	1	1	15
Cooker	2	0	0	0	2
Chemical	0	1	0	0	1
Cigarettes	1	1	0	0	2
Hot pipe	0	0	1	0	1
Heater	1	0	0	0	1
Unknown	0	1	0	1	1
Relation to independence and seizure frequency:					
Burns/100 people (n):					
Independent	9	1.8	1.8	3.6	16.2
Intermediate	5.3	4.3	0	2.1	11.7
Dependent	2	2	1	0	5
Burns/seizure ( $\times 10^{-4}$ ) (n):					
Independent	21	4.2	4.2	8.4	37.8
Intermediate	18	15	0	7.5	40.5
Dependent	14	14	7	0	35
Seizures/person/year (median):					
Independent	43				
Intermediate	28				
Dependent	14				

consequence, however, is that the effectiveness of simple interventions can be gauged in a large population.

This case record survey of burns at the Chalfont Centre for Epilepsy is unique in that it included all burns and had an accurate record of the cause in most cases. The seizure charts kept prospectively by staff and residents allowed the frequency of burns per seizure to be calculated. The data are considered to be reasonably accurate as all but the most trivial burns were recorded. Brief, inconspicuous seizures may not have been recorded, particularly simple partial, absence seizures or myoclonic jerks. All complex partial, secondary generalised, and generalised tonic-clonic seizures would, however, have been noted. From the 303 patients there were a total of 34 burns, at least 19 of which were seizure related, and 18 631 seizures were recorded during the 1 year period. Only one required skin grafting but six required over 3 weeks to heal. Therefore only one in every 980 seizures resulted in a burn with one in 3105 resulting in a burn taking longer than three weeks to heal.

Although there were significantly more burns in independent houses, there were also a greater number of seizures per person on average in this group. As most burns were related to seizures, correcting for the number of seizures per person abolished the significance of level of independence on number of burns.

It is of note that almost no burns occurred secondary to showers or heating devices, which is in stark contrast with all previous reports. Five years ago thermostatic regulators were put on to hot water supplies and covers were installed to protect hot water pipes and heating appliances. These changes followed several severe burns in previous years from the above sources.

A further difference between this study and previous, community based studies was that there were very few cooking related burns in this study. This is almost certainly due to the fact that even the most independent residents do relatively little cooking as a canteen is available at lunchtimes and residents are encouraged to use microwave ovens.

Lastly, most burns were caused by hot drinks; either severe burns from large containers of hot water such as kettles or teapots, or milder burns from individual cups. The scope for reducing future morbidity from burns in persons with epilepsy is therefore in this area. The use of microwave ovens to heat individual cups of hot water is one option as these were already in widespread use for food preparation. The use of insulated flasks instead of teapots would prevent surface burns and the exit valve would prevent hot water being spilt. Further, hot water heaters, which are only able to dispense a fixed amount of water, are available and would be an alternative to kettles.

Burns are therefore a relatively rare but potentially serious cause of morbidity in people with epilepsy. The more severe burns are also largely preventable by simple interventions, which do not interfere greatly with a person's independence.

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#### **A quartet of Down's syndrome, Alzheimer's disease, cerebral amyloid angiopathy, and cerebral haemorrhage: interacting genetic risk factors**

Since 1993 the  $\epsilon 4$  allele of apolipoprotein E (apoE) on chromosome 19 has been recognised as the major genetic risk factor for sporadic Alzheimer's disease. Deposition of amyloid  $\beta$  protein (A $\beta$  protein) in the cerebral cortex is a key feature of Alzheimer's disease and may be of pathogenetic importance. Sporadic cerebral amyloid angiopathy often coexists with Alzheimer's disease and involves the deposition of A $\beta$  protein in leptomeningeal and cortical blood vessels. Both conditions may occur in Down's syndrome, presumably because of the increased expression of  $\beta$ -amyloid precursor protein (APP) associated with trisomy 21, the chromosomal location of the APP gene.

Intracerebral haemorrhage is the principal, though uncommon clinical manifestation of cerebral amyloid angiopathy. Studies have suggested that the apoE  $\epsilon 2$  allele and also the  $\epsilon 4$  allele may occur more often in patients with cerebral amyloid angiopathy related haemorrhage.<sup>1,2</sup> We report, to our knowledge, only the second case of cerebral amyloid angiopathy related haemorrhage in Down's syndrome and suggest that the patient's neuropathology and clinical manifestations were modulated by interacting influences of the APP and apoE genes.

A 46 year old man with Down's syndrome was found dead in his bed. There were no suspicious circumstances. He had a long history of well controlled absence seizures on 800 mg sodium valproate a day. One month before his death he had had a left lower lobe pneumonia, from which he recovered well with intravenous antibiotic. He was cognitively impaired with some deterioration in behaviour in the last few years of his life, necessitating placement in care. There was no family history of dementia or intracerebral haemorrhage. He took no antiplatelet or anticoagulant medication and was not hypertensive. A necropsy was performed.

The patient had a typical Down's syndrome facies. No head injury was apparent. There was evidence of bronchopneumonia in the left lung. There was no significant coronary atheroma and no evidence of congenital heart disease. Neuropathological examination disclosed a small brain (940 g) with a band of haemorrhage in the subarachnoid space overlying the frontal and parietal lobes of the right cerebral hemisphere. Coronal sections disclosed a large haematoma 7 cm $\times$ 5.5 cm $\times$ 5.5 cm lying superficially in the hemisphere beneath the subarachnoid haemorrhage. The middle third of the right cerebral hemisphere was expanded with a 5 mm shift of the midline structures and a supracallosal hernia to the left. There was extensive secondary haemorrhage into the tegmen-

tum of the midbrain and upper pons, as a consequence of brainstem compression due to raised intracranial pressure.

Histological examination of sections of cerebral neocortex stained by silver impregnation (modified Bielschowsky's stain) disclosed numerous non-neuritic plaques and sparse neuritic plaques. There were scanty neurofibrillary tangles. The age related neuritic plaque score and history of dementia gave a "definite" neuropathological diagnosis of Alzheimer's disease according to the criteria of the Consortium to Establish a Registry for Alzheimer's disease (CERAD). In sections from the haematoma wall there was extensive acute ischaemic necrosis in addition to the haemorrhage. Immunostaining for A $\beta$  protein (Dako mouse monoclonal antibody raised to residues 8–17 of A $\beta$  protein) confirmed the presence of multiple plaques within the cortical ribbon and showed severe amyloid deposition in many blood vessels within the cortex and overlying meninges. Some blood vessels had narrowed lumens and others displayed a "double barrel" appearance, typical findings in cerebral amyloid angiopathy associated vasculopathy. There was microscopical evidence of previous haemorrhage in the form of multiple small intracortical glial scars with haemosiderin pigment in macrophages. In the sections examined there was no evidence of fibrinoid necrosis.

The apoE genotype of the patient was  $\epsilon 2/\epsilon 4$ , determined by analysis of DNA extracted from formalin fixed paraffin embedded brain tissue as described previously.<sup>1</sup>

Only once before has a cerebral amyloid angiopathy related haemorrhage been reported in a patient with Down's syndrome and Alzheimer's disease.<sup>3</sup> Indeed an analysis of death certificates listing Down's syndrome as the underlying or a contributing cause of death did not document intracerebral haemorrhage among 793 cases examined from the United States during 1976.<sup>4</sup> This seems surprising as Down's syndrome is associated with both Alzheimer's disease and cerebral amyloid angiopathy, the second predisposing to intracerebral haemorrhage. The studies on our patient may suggest some reasons why the expected quartet of findings is a rare but aetiologically related occurrence.

Patients with Down's syndrome have a shorter life expectancy because of excess mortality from haemopoietic malignancies, congenital heart defects, and respiratory tract infections.<sup>4</sup> Although there is "premature" Alzheimer's disease in Down's syndrome, predisposition to these other conditions can have an early fatal outcome.

Our patient was predisposed to Alzheimer's disease not only because of his extra copy of the APP gene, but also because of his apoE  $\epsilon 4$  allele. By the age of 40, virtually all patients with Down's syndrome have neuropathological changes characteristic of Alzheimer's disease. The increased dosage of the APP gene has been shown to produce increased serum concentrations of APP and the two major forms of A $\beta$  protein—A $\beta$ 40 and A $\beta$ 42. The  $\epsilon 4$  allele increases the risk of dementia in patients with Down's syndrome. Indeed the combination of Down's syndrome with the  $\epsilon 4$  allele leads to very high deposition of A $\beta$  protein in plaques.<sup>5</sup> Possession of the  $\epsilon 4$  allele also predisposes to deposition of A $\beta$  protein in the cerebral leptomeningeal and cortical vasculature. Evidence currently suggests that the  $\epsilon 2$  allele, although protective against Alzheimer's disease, pre-

disposes to haemorrhage due to cerebral amyloid angiopathy.<sup>1,2</sup> We previously found more than a threefold overrepresentation of both the  $\epsilon 2$  allele and the 2/4 genotype in patients with cerebral amyloid angiopathy related haemorrhage and speculated that whereas  $\epsilon 4$  is a risk factor for deposition of A $\beta$  protein in blood vessel walls,  $\epsilon 2$  is a risk factor for haemorrhage from amyloid laden blood vessels.<sup>1</sup> Although  $\epsilon 2$  and  $\epsilon 4$  alleles are neither necessary nor sufficient for cerebral amyloid angiopathy related haemorrhage, these apoE alleles seem to be major susceptibility polymorphisms for cerebral amyloid angiopathy ( $\epsilon 4$ ) and cerebral amyloid angiopathy related haemorrhage ( $\epsilon 2$ ). Because the  $\epsilon 2$  allele is only 8% of the apoE alleles in the population, including the subgroup of patients with Down's syndrome, it does not commonly coexist with the more closely related conditions of Alzheimer's disease, cerebral amyloid angiopathy, and Down's syndrome to produce cerebral haemorrhage.

In conclusion, we suggest that in this patient with Down's syndrome, three copies of the APP gene, possession of the apoE  $\epsilon 4$  allele, and age (46 years) predisposed to Alzheimer's disease and cerebral amyloid angiopathy whereas the apoE  $\epsilon 2$  allele predisposed to haemorrhage from the amyloid laden blood vessels.

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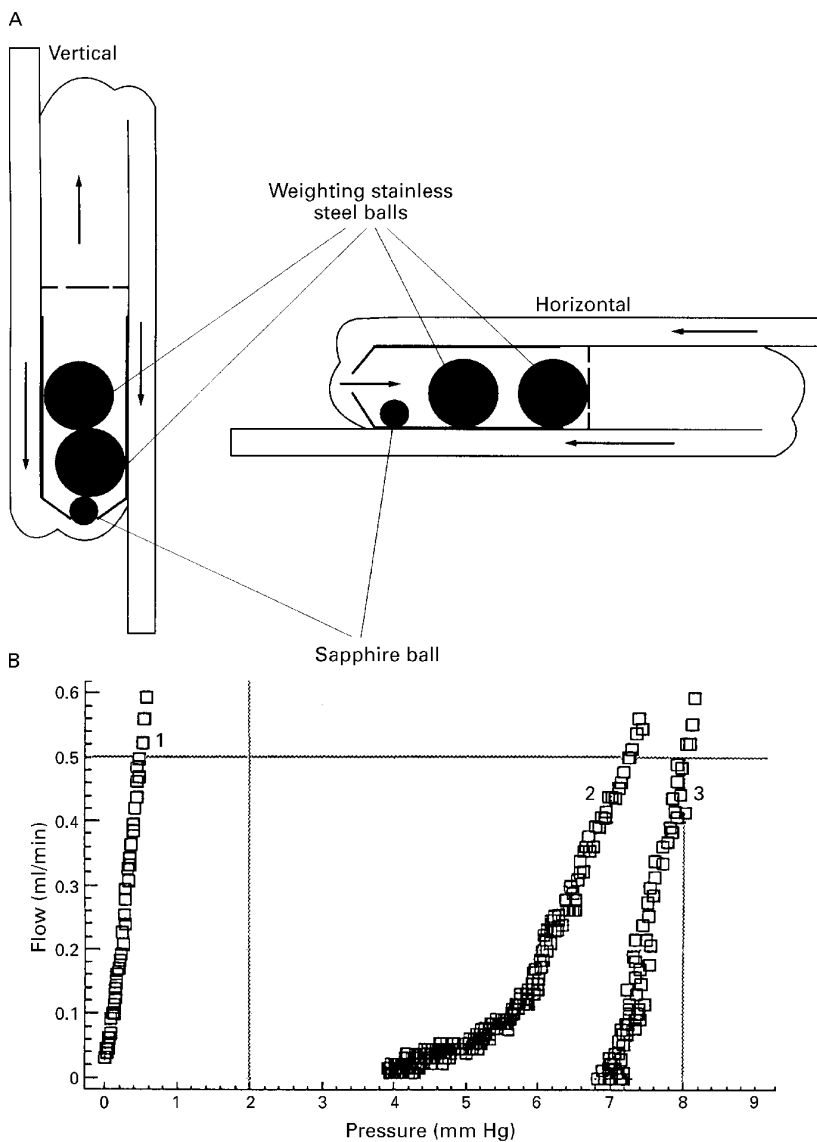
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### Chhabra hydrocephalus shunt: lessons for gravitational valves

Overdrainage is a significant clinical problem after shunting for hydrocephalus as confirmed by the UK Shunt Registry.<sup>1</sup> Various devices have been developed to reduce the rate of CSF drainage in the upright position which have been assessed by the UK Shunt Evaluation Laboratory.<sup>2</sup> The average price of a shunt varies from £175 to £650 in the United Kingdom. Surprisingly, the prices are higher in the developing countries.<sup>3</sup> However, some local lower cost constructions are available and are reported to function well.<sup>4</sup>



(A) Diagram of the Chhabra shunt. Two weighting balls control the opening pressure, depending on whether the body position is vertical or horizontal. (B) Pressure-flow performance curves of two-ball Chhabra shunts in the horizontal (1) and vertical (2,3) body positions. Curve 2 was recorded when the pressure pulsations of magnitude 7 mm Hg peak to peak and frequency 20/min were superimposed on a slowly changing static pressure. Each point represents 2 minutes average of flow (plotted along y axis) and pressure (x axis).

The Chhabra shunt is a low cost device, developed and manufactured in India, that incorporates a gravitational siphon preventing mechanism. In the vertical position one, two, or three (depending on performance level) stainless steel weighting balls press on a sapphire ball which closes the CSF flow aperture, increasing the shunt's opening pressure (figure (A)). In the horizontal position the opening pressure is theoretically equal to zero mm Hg, as the balls fall away. A similar principle is applied in constructions of other "gravitational" shunts—namely, the Cordis horizontal-vertical LP valve, the newly designed dual-switch Miethke valve (Germany) and the Fuji, another low cost valve (Philippines).

We tested a sample of two Chhabra medium pressure shunts (containing two balls) using a 2 week evaluation protocol.<sup>2</sup> Our main aim was to investigate the impact of posture (horizontal-vertical) on shunt pressure-flow performance. We also investigated how the fluctuations in proximal

pressure, simulating the presence of naturally occurring waves of intraventricular pressure, may alter shunt function. Such waves may occur not only due to heart and respiratory function but also due to body movements during walking, jogging, etc.

The figure (B) shows two typical pressure-flow performance curves recorded in the horizontal and the vertical position. They represent two almost straight parallel lines. Their slopes depict the low hydrodynamic resistance of the shunt (1.3 mm Hg/ml/min). This is much lower than the physiological resistance to CSF outflow, which normally lies within the range 6–10 mm Hg/ml/min.<sup>5</sup> The average operating pressure determined for the vertical shunt position was around 7 mm Hg and for the horizontal position it was 0.6 mm Hg. The area between these lines represents the possible operating range in all the intermediate body positions. Therefore, we conclude that the operating pressure of the shunt varies with the body position, as intended.

The main problem with this valve arises when the patient moves upwards and downwards. Such a situation has been simulated by the addition of a pulsating waveform of variable amplitude to the proximal pressure (frequency was controlled from 90 revolutions/min to 5/min). As a result, the lower end of the pressure-flow performance curve was consistently twisted to the left (towards lower pressures, figure (B)). In vivo, variations in intraventricular pressure, produced by either an increased magnitude of the pulse waveform or repeated body movement, may accelerate the drainage rate, in some cases possibly leading to overdrainage. The above phenomenon is probably a common feature of all gravitational valves, which should always be implanted with caution, taking into account the usual risk factors for serious consequences from overdrainage (thin cerebral mantle and a high brain compliance) and the possible lifestyle of the patient after surgery.

Contrary to other gravitational valves, the Chhabra shunt does not have any valve working with the weighting balls that would prevent the reflux of CSF from the peritoneal cavity to the ventricles. Therefore, CSF reflux is possible, undoubtedly in the upside down and also in the horizontal body position (albeit at a lower rate).

The behaviour of the valve in a strong magnetic field (1.5 T) does not exhibit any alarming variation. However, the artefact on MRI may be considerable.

In conclusion, the intentions of the designers of the Chhabra shunt to make it operate at a higher operating pressure in the vertical than the horizontal body position were confirmed during this evaluation. The shunt has a repeatable pressure-flow performance that does not differ from the performance of more expensive valves manufactured by the big western corporations. However, because the shunt has a very low resistance to flow, overdrainage may be a problem depending on the patient's life activity. Reflux of CSF from the peritoneal to the ventricular cavity is possible.

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# A case of chronic paroxysmal hemicrania responding to subcutaneous sumatriptan

Chronic paroxysmal hemicrania was first described by Sjaastad and Dale in 1974.<sup>1</sup> It is characterised by attacks of excruciating unilateral oculotemporal pain associated with autonomic changes, such as lacrimation, rhinorrhea, ptosis, miosis, and conjunctival suffusion. It differs from cluster headache for its female predominance, brevity (5–45 minutes), and frequency (5–20/day) of pain attacks, as well as for its response to indomethacin in doses of up to 150 mg/day.<sup>2</sup> Experience with subcutaneous sumatriptan in chronic paroxysmal hemicrania is scarce. Here we report on the effect of subcutaneous sumatriptan in a patient with chronic paroxysmal hemicrania.

In May 1994, when 34 years old, this previously healthy woman started to have attacks of severe temporal and periorbital pain usually associated with conjunctival injection, lacrimation, ptosis, eyelid oedema, and nasal congestion. Frequency and duration of attacks were variable. She experienced at least five pain attacks a day from the beginning of her clinical presentation, but every few months the frequency increased up to more than 20 episodes each day in bouts lasting 20–30 days. The duration of attacks ranged from several minutes to 1 hour. A diagnosis of cluster headache was made. She was treated with the maximum doses that she could tolerate of verapamil (40 mg/6 h), and methysergide (1 mg/6 h), without success. Ergotamine (2 mg at night) was added with doubtful symptomatic improvement, so domiciliary 100% oxygen (7 l/min) and/or subcutaneous sumatriptan (6 mg) were prescribed. She thought that oxygen inhalation during the attacks did not stop the pain but alleviated it if the episode was mild and if the oxygen was taken during the earliest part of the attack. Subcutaneous sumatriptan stopped the attacks in less than 15 minutes. In addition, during the bouts, when she experienced multiple consecutive pain attacks, the patient noticed that after subcutaneous sumatriptan she was free of pain for a maximum of 8 hours and a minimum of 6 hours. She was sent to us in March 1996. Systemic and neurological examinations, as well as high resolution brain CT (with and without contrast) were unremarkable. Indomethacin (75 mg daily), was started, with absolute effectiveness after 4 days. Indomethacin has been withdrawn twice, with immediate pain reappearance. During more than one year of follow up, she has twice needed to increase indomethacin up to 125 mg daily for several weeks because of further pain episodes, which promptly stopped with subcutaneous sumatriptan on the four occasions that this was injected. She is now taking 75 mg indomethacin daily and ranitidine, with very infrequent attacks of only slight pain.

The differential diagnosis between chronic paroxysmal hemicrania and chronic cluster headache still poses some problems. With that in mind, this woman clearly meets the criteria of the International Headache Society classification for diagnosis of chronic paroxysmal hemicrania.<sup>2</sup> Subcutaneous sumatriptan consistently relieved her chronic paroxysmal hemicrania attacks in less than 15 minutes and protected her from further pain attacks for 6 to 8 hours. Subcutaneous sumatriptan is a very effective symptomatic treatment for cluster headache pain attacks,

this confirming that trigemino-vascular activation with cranial vasodilatation or plasma protein extravasation are the pathophysiological explanation for cluster headache attacks.<sup>3</sup> The aetiology and pathogenesis of chronic paroxysmal hemicrania are still unknown. Goadsby and Edvinsson have recently reported a patient with chronic paroxysmal hemicrania in whom concentrations of calcitonin gene related peptide and vasoactive intestinal polypeptide, two markers of trigemino-vascular activation, were raised in the cranial circulation during attacks. Moreover, the concentrations of both peptides became normal when indomethacin was given, all this suggesting a shared pathophysiology between chronic paroxysmal hemicrania and cluster headache.<sup>4</sup> The finding of the effect of subcutaneous sumatriptan in chronic paroxysmal hemicrania clarifies this point further. To the best of our knowledge, the effect of subcutaneous sumatriptan has been reported only in three patients with chronic paroxysmal hemicrania and gives discordant results.<sup>5–7</sup> One patient, a male but with very typical chronic paroxysmal hemicrania attacks, did not respond to subcutaneous sumatriptan on two different occasions, although the duration of this patient's attacks was not mentioned.<sup>5</sup> Two other patients had a clearly positive response.<sup>6,7</sup> These two patients, however, were atypical, one also having intracranial hypertension and the other both chronic paroxysmal hemicrania and trigeminal neuralgia. Although more experience is necessary, our findings suggest that, in parallel with migraine and cluster headache, trigemino-vascular activation also occurs in chronic paroxysmal hemicrania.

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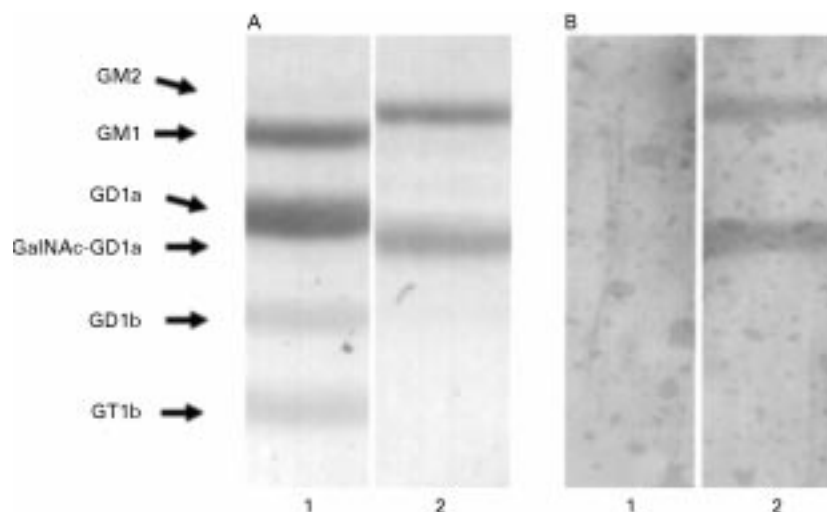
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## IgM anti-GM2 antibody in a patient with Guillain-Barré syndrome subsequent to cytomegalovirus hepatitis cross reacts with N-acetylgalactosaminyl GD1a

Anti-GM2 antibodies are associated with acute cytomegalovirus infection in patients with Guillain-Barré syndrome.<sup>1,2</sup> Irie *et al*<sup>1</sup> reported that anti-GM2 antibodies do not

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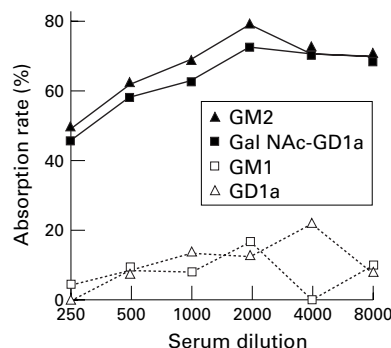
**Figure 1** Binding of gangliosides with serum IgMs from a patient with Guillain-Barré syndrome subsequent to acute cytomegalovirus hepatitis. Lane 1: bovine brain gangliosides GM1, GD1a, GD1b, and GT1b. Lane 2: purified GM2 and GalNAc-GD1a. (A) Thin layer chromatography plate stained with orcinol. (B) Chromatogram immunostained after overlaying it with serum from the patient (1:100) then with peroxidase conjugated antihuman IgM (Dako, Denmark; 1:1000). The chromatography plates were developed in a solvent system of chloroform/methanol/ 12mM magnesium chloride in water (5:4:1, volume). The IgMs from the patient reacted specifically with the GM2 and GalNAc-GD1a.

bind to N-acetylgalactosaminyl GD1a (GalNAc-GD1a), a terminal trisaccharide identical to that of GM2. Jacobs *et al*<sup>2</sup> did not test whether IgM anti-GM2 antibodies react with GalNAc-GD1a. By contrast, Kusunoki *et al*<sup>3</sup> reported that a patient with Guillain-Barré syndrome had IgM antibody activity against both GalNAc-GD1a and GM2, but in whom no result of anti-CMV antibody was shown. We had a patient with Guillain-Barré syndrome subsequent to acute cytomegalovirus hepatitis who had IgM antibodies both to GM2 and GalNAc-GD1a. We investigated whether the IgM anti-GM2 antibodies cross react with GalNAc-GD1a.

Three days after an episode of stomatitis, a 32 year old man noticed left sided facial weakness and dysaesthesia distally in his feet. Over a day, the facial weakness extended to the right side and dysaesthesia progressed to the limbs. He developed progressive weakness of the limbs on day 4, and the next day was unable to stand. On day 5, the patient presented with facial diplegia, severe limb weakness, and moderate reduction of superficial sensation distally in all four limbs. The respiratory muscles were slightly affected. Deep tendon reflexes were absent. Liver enzyme concentrations were raised slightly. Protein concentration in CSF was 109 mg/dl and cellularity was normal. High IgM anti-CMV antibody titres were found in both serum and CSF by enzyme linked immunosorbent assay (ELISA). An electrophysiological study suggested that the predominant process was demyelination involving the motor nerves. Right ulnar sensory nerve action potential was absent. Visser *et al*<sup>4</sup> reported that patients with Guillain-Barré syndrome with associated cytomegalovirus were young and often developed severe sensory loss with facial nerve involvement and respiratory insufficiency. They also reported a strong correlation between cytomegalovirus infection and severe sensory loss. The clinical manifestations in our patient were similar to those reported by Visser *et al*.

Thin layer chromatography with immunostaining showed that the serum IgM from our patient reacted strongly with GM2 and

GalNAc-GD1a, but not with GM1, GD1a, GD1b, or GT1b (fig 1). ELISA confirmed that his serum had high titres of IgM antibodies to GM2 (1:25 600) and to GalNAc-GD1a (1:12 800) on day 4. Plasmapheresis was performed on days 5, 8, 24, 27, and 29, he was able to walk without assistance on day 60, but his facial diplegia showed slow improvement. The IgM anti-GM2 (1:800) and anti-GalNAc-GD1a (1:400) titres in this patient were significantly reduced on day 39. In the absorption study his serum was added to separate wells coated with individual ganglioside antigens (GM2, GalNAc-GD1a, GM1, and GD1a). The absorption rate was calculated from (1-(optical density at 492 nm in the well with serum with absorption treatment)/(optical density in the reference well with serum without absorption treatment)). No IgM anti-GM2 antibody was absorbed by GM1 or GD1a (fig 2). By



**Figure 2** Absorption study of serum IgM anti-GM2 antibody from the patient carried out with GM2, GalNAc-GD1a, GM1, and GD1a. Serum samples were diluted serially from 1:250 to 1:8000 and added to wells coated with 5 pmol portions of each ganglioside antigen. The absorption rate was calculated from (1-(optical density at 492 nm in the well with serum with absorption treatment)/(optical density in the reference well with serum without absorption treatment)). The IgM anti-GM2 antibody in our patient was not absorbed by GM1 and GD1a but was by GM2 and GalNAc-GD1a.

contrast, IgM anti-GM2 antibody was absorbed by GalNAc-GD1a. Larger studies are needed to confirm whether (1) some patients with Guillain-Barré syndrome after CMV infection have IgM anti-GalNAc-GD1a antibody and (2) that the anti-GalNAc-GD1a antibodies cross react with GM2.

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## Electrophysiological recordings in bilateral hemifacial spasm

Hemifacial spasm typically consists of unilateral involuntary spasms of the mimic muscles innervated by either facial nerve. There is some controversy whether mechanical irritation of the facial nerve entry zone by vessels in the cerebellopontine angle or hyperexcitability of the facial nerve nucleus is the main cause of this problem.<sup>1,2</sup> To our knowledge, only two cases of bilateral hemifacial spasm have been described in some clinical detail but without electrophysiological recordings.<sup>3,4</sup> The mechanism underlying the bilateral occurrence of spasms has not been investigated so far: either hyperexcitability of a facial nerve nucleus spreading to the contralateral side or independent mechanical irritation of both nerves might be involved. We report a patient with predominantly left sided spasms, electrophysiological diagnosis of bilateral facial spasm, the clinical course after surgical treatment according to MR evidence of elongated vertebral and basilar arteries, and implications of electrophysiological recordings on the pathogenesis of bilateral hemifacial spasm.

This 60 year old male patient presented with a history of gradually increasing left eye twitching over the past few years. He did not notice involvement of other facial muscles or of associated symptoms such as hearing deficits, vertigo, or headache. Visual inspection showed frequent clonic involuntary synchronous contractions of his left orbicularis oculi and left orbicularis oris muscles. On voluntary contraction of the orbicularis oculi muscle, there was some synkinesis of the left orbicularis oris

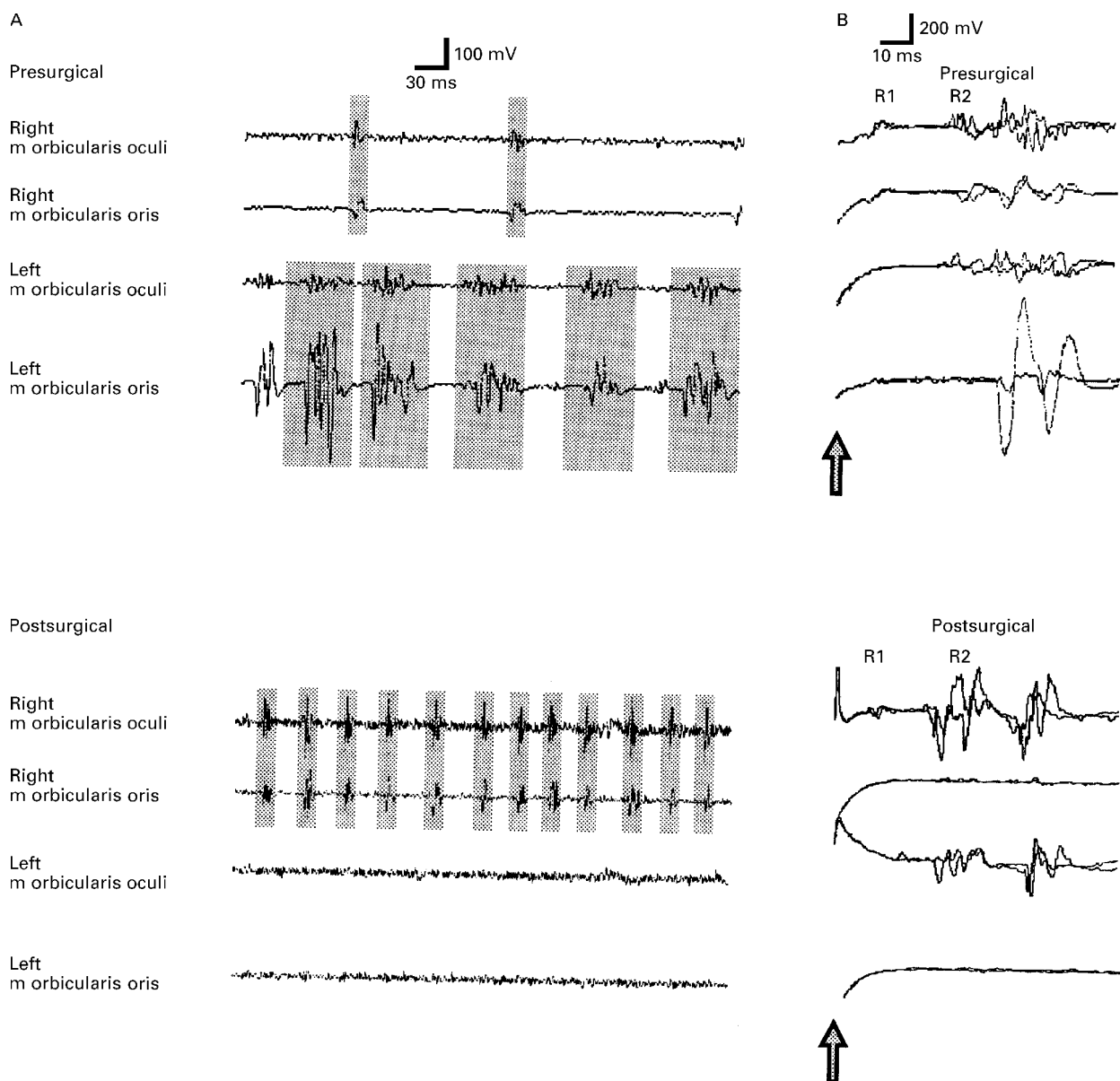
muscle and vice versa. There was no weakness of facial muscles or other neurological deficit. Four channel surface EMG recording from facial muscles was performed to ascertain the suspected diagnosis of left hemifacial spasm. Recordings gave evidence of irregular and asynchronous spasms of left and right facial muscles with higher frequency, amplitude, and longer duration on the symptomatic left side (fig 1A). Blink reflex recordings with stimulation of either supraorbital nerve showed bilateral R2 components also involving the orbicularis oris muscles of both sides (fig 1B); latencies of R1 and R2 components were in the normal range. Magnetic resonance imaging showed a grossly distended vertebral and basilar artery approaching first the right cerebellopontine angle and later in its course also the left cerebellopontine angle before taking its normal median position in its rostral segment (fig 2). This extraordinary course suggested a

possible mechanical irritation of both facial nerves.

The patient thus had a neurovascular decompression on the symptomatic left side. During surgery, close contact of the basilar artery with nerve entry zones of the left facial and vestibulocochlear nerve was found. After interposition of a piece of ivalon sponge, spasms of the left facial muscles disappeared almost completely leaving a slight left facial nerve paresis which cleared completely over the next months without functional deficit. There was a partial hearing loss on the operated side. Electrophysiological control recordings 4 months after surgery showed a reduction of the amplitude of compound muscle action potentials recorded from the left orbicularis oculi muscle. There was also a loss of facial synkinesis on the operated side, whereas spontaneous spasms and synkineses of the right facial muscles remained un-

changed or even slightly increased (fig 1A). Right sided spasms have become more prominent also during clinical investigation; they have, however, so far not bothered the patient enough to warrant an additional contralateral operation.

Bilateral twitching of facial muscles most commonly occurs in blepharospasm; this focal dystonia may occasionally mainly present by contractions of the orbicularis oculi muscle of only one side as experienced by our patient. Even more so, in patients with bilateral hemifacial spasm a dystonic aetiology may be erroneously attributed and lead to unsuccessful treatment.<sup>3</sup> Needle EMG recordings can be helpful in discriminating these diseases by showing unphysiologically high frequent discharges of motor units in hemifacial spasm.<sup>5</sup> With surface electrodes, simultaneous electrophysiological recording from facial muscles of both sides can differentiate this disorder from



**Figure 1** Four channel surface EMG recording from orbicularis oculi and oris muscles. (A) Spontaneously occurring spasms of facial muscles. EMG bursts are synchronous on each side (representing synkinesis) but asynchronous with regard to the contralateral side. Before surgery, bursts are more frequent, of higher amplitude and duration on the clinically symptomatic left side. After surgery, spasms occurred only on the right side at increased frequency. (B) Blink reflex with electrical stimulation of the right supraorbital nerve. Before surgery, R1 components appear in both muscles on the stimulated side, R2 components are seen synchronously on both sides thus also involving the contralateral orbicularis oris muscle (same phenomenon also with stimulation on the left side). After surgery, synkinesis of the orbicularis oris muscles has disappeared. Arrow=time of stimulation.



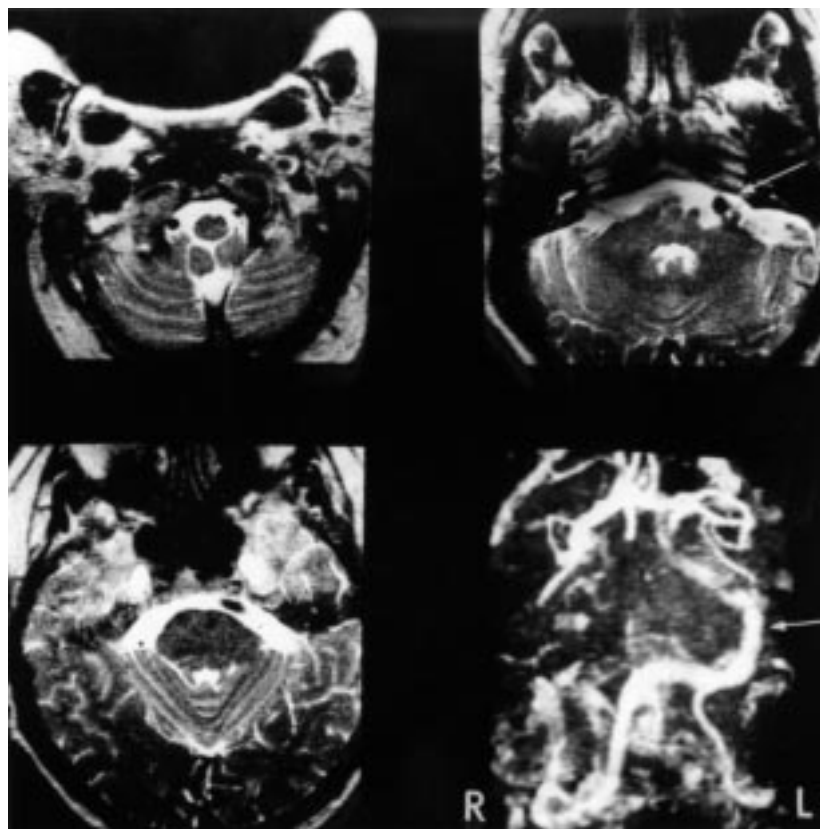


Figure 2 Axial T2 weighted MR sections and MR angiography (lower right panel) of brain stem and vertebrobasilar arteries. The left vertebral artery is hypoplastic (upper left and lower right). The larger right vertebral artery turns left over the midline and the caudal basilar artery (arrow) lies in the left cerebellopontine angle in close proximity to cranial nerves VII and VIII. A small vessel crosses these cranial nerves in the right cerebellopontine angle (upper right). At the midpontine level, the basilar artery turns back to midline (lower left).

the rare bilateral hemifacial spasm by showing synchronous twitching of the muscles innervated by each facial nerve but asynchrony of muscle twitching between right and left facial muscles. In normal subjects and on the unaffected side of patients with unilateral hemifacial spasm R2 components of the electrical blink reflex are restricted to both orbicularis oculi muscles, but additional facial muscles are usually involved in patients with hemifacial spasm. This synkinesis of other muscles, which was found in this patient bilaterally, could be due to ephaptic transmission at the nerve entry zone or to facial nerve nucleus hyperexcitability; the immediate postoperative disappearance of synkinesis and abnormal R2 spread found in this case would thus be compatible with either suppression of ephaptic transmission at the nerve entry root or reduction of secondary facial nerve nucleus hyperexcitability. Both the asynchrony of spontaneous muscle bursts and the persistence or even increase of spasms on the less affected side after contralateral successful surgery in our case suggest independent trigger mechanisms on both sides most probably due to bilateral nerve entry zone irritation by aberrant vessels. Even with irritation of the nerve entry root being the probable primary cause, hyperexcitability of brain stem nuclei may also play a part; the reduced contralateral R2 component of the orbicularis oris muscle of the side contralateral to surgery (fig 1B) might be due to a loss of facilitatory effect of the operated side on the generation of this response.

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## CORRESPONDENCE

### Depression and its relation to lesion location after stroke

The documentation of a 20% prevalence of depression after stroke<sup>1</sup> has important therapeutic implications for patients with significant ischaemic heart disease and/or cardiac arrhythmia coexisting, either coincidentally or in an aetiopathogenetic role, with stroke illness. In such patients therapeutic choices

now need to be governed by the recognition that, despite comparable therapeutic benefit, adverse cardiac events such as sinus tachycardia, severe angina, and ventricular ectopy, are more likely to occur after tricyclic drugs such as nortriptyline, than after selective serotonin reuptake inhibitors such as paroxetine ( $p < 0.03$ ).<sup>2</sup> Whereas nortriptyline causes a sustained increase in heart rate and a reduction in heart rate variability,<sup>2</sup> the second being a marker of increased cardiac mortality risk,<sup>3</sup> no such sequelae occur after paroxetine.<sup>2</sup>

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- 1 MacHale SM, O'Rourke SJ, Wardlaw JM, *et al.* Depression and its relation to lesion location after stroke. *J Neurol Neurosurg Psychiatry* 1998;64:371-4.
- 2 Roose SP, Laghrissi-Thode F, Kennedy JS, *et al.* Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 1998;279:287-91.
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### MacHale replies:

We wholeheartedly agree with Jolobe's comments on the need to treat depressive illness after stroke with appropriate antidepressant drugs that have a low risk of cardiovascular side effects. Other studies using trazodone<sup>1</sup> and other selective serotonin reuptake inhibitors such as citalopram<sup>2</sup> have shown that these are safe and effective in the treatment of this condition. Unfortunately, the problem remains that the vast majority of patients with depressive illness after stroke remain untreated. Despite clear evidence of negative effects on recovery in functional status and cognitive performance<sup>3</sup> it has been shown that inadequate and insufficient efforts at treatment had not influenced the prevalence of depression up to 5 years after stroke.<sup>4</sup> The first important step therefore seems to be to encourage clinicians to recognise and treat depression after stroke, the second being to educate them about which are the appropriate medications to prescribe.

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- 1 Reding M, Orto L, Winter S, *et al.* Antidepressant therapy after stroke. A double-blind trial. *Arch Neurol* 1986;43:763-5.
- 2 Andersen G, Vestergaard K, Lauritzen. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994;25:1099-104.
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## BOOK REVIEWS

**Epilepsy and other Neurological Disorders in Coeliac Disease.** Edited by G GOBBI, F ANDERMANN, S NACCARATO, AND G BANCHINI. (Pp396, £65.00) Published by John Libbey Co, London, 1997. ISBN 0-86196-537-X.

In Soho, there used to be a restaurant called Fatso's. Here you could eat as many bowls of different pastas with creamy sauces as you could manage for a fixed price. I feel sure that I made a major contribution to its bankruptcy, quite soon after opening. Now, as well as the high fat intake I learn I have exposed myself to increased risk of epilepsy, cerebral calcifications, dementia, peripheral axonal neuropathy, schizophrenia, anxiety, and depression. For these are some conditions apparently associated with coeliac disease and the risk of coeliac disease seems to be greatest in those consuming large amounts of gluten in wheat products, especially pasta. The most interesting chapter tracks the evolution of human diet from hunter-gatherers to farmers, the growth of gluten as a foodstuff and relation to gluten intolerance in different populations, especially in association with the associated HLA-B8 genotype. There are some more general chapters early on discussing current concepts of gluten intolerance and pathogenesis of coeliac disease. The neurology of this area is only just being uncovered and the remainder of the book comprises short papers and case reports that introduce the possible range of the disease. The papers are illustrated by some good quality scans, and clinical and pathological photographs. The book should be seen as an introduction to a field and as a collection of papers it is inevitably fragmentary. Nevertheless, it is a shame that there is no attempt at a unifying chapter and it is difficult to take away any clear message from the book. It will prove useful to neurological libraries as a source to which to refer with comprehensive access to the literature. I came away hoping that at least I had drunk enough Chianti to counter the effects of the saturated fats.

MARK MANFORD

**Human Brain Function.** By R S J FRACKOWIAK, K J FRISTON, C D FRITH, R J DOLAN, AND J C MAZZIOTTA. (Pp 528). Published by Harcourt Brace and Co, San Diego, California, 1997. ISBN 0-12-2648404.

This book is a pleasure to read, either as a reference book or as a progressive journey through a decade of development in this field. The preface makes the point that it is time to take stock and to reflect on different approaches, including the philosophy of localisation and the contrasting issues of functional integration. It also reiterates the principle that these are relatively new methods and that they have not created a new science. Instead it is intended that much of the work has been selected on the principal of testing new or traditional hypotheses in human subjects to provide a coherent view, rather than an encyclopaedic review.

It is divided into three parts, concentrating mainly on PET. The first is probably the most useful and covers principles and methodology, dealing with the conceptual basis for the remainder of the book. This includes a description of some of the important mathematics: in an initial overview, the principles of functional organisation and the implications for imaging are summarised and then followed by a description of statistical parametric mapping and other components of functional imaging data analysis. This is extended in the chapters that follow in a way that reflects the development and application of these approaches over the past decade.

Topics include the spatial transformation of images and the way that this can be used to reduce differences and facilitate comparisons, to characterise differences in topography, or to restore and segment images. The additional statistical challenges involved in fMRI are touched on and a guide is offered for the selection of different tests, sensitivity and specificity, choice of parameters, etc. Methods for describing distributed functional systems are suggested, with approaches to functional integration. This first part of the book is concluded with a useful taxonomy for study design which returns to the importance of interactions as well as focal activations.

Part two deals with studies that have been completed by authors and their collaborators and by other international groups. It incorporates a systems approach modelled around visual, somatosensory, motor, and memory systems, functional recovery, reading, and neuromodulation. Part three of the book looks ahead and includes a discussion of integrating new developments in the applications of maps and atlases, the contribution of fMRI, and then proposes a philosophical framework for the future.

The large scale nature of research in this domain has sometimes created an impression in those outside the field that it is dominated by technology or phenomenology rather than a philosophy of considering functional neurobiological questions. This book makes a strong argument for the second, by describing important complexities in experimental design and how their selective use has been very productive over the past decade and provided a basis for the next. I recommend it to all those with a strong interest in this field.

SIMON BONIFACE

#### **Traumatic Brain Injury Rehabilitation.**

Second edition. Edited by MARK YLVISAKER. (Pp 479, £45.00). Published by Heinemann, Oxford, 1998. ISBN 0-7506-9972-8.

This book is written mainly by an assistant professor of communication disorders, with contributions from 28 speech therapists, psychologists, doctors, physiotherapists, occupational therapists, and educators from different centres across the United States. It emphasises important principles of multidisciplinary management of patients with brain injuries and their families in general. But of more importance, it is one of only a few books dealing with children and their particular problems, the others being either older, or having much greater emphasis on epidemiology and outcome, or on the educational implications of injury.

The content can be roughly divided into 25% medical, nursing, speech, and swallowing assessment, 33% cognitive rehabilitation, 25% behavioural management, social reintegration, family support, and education, and 12% re-entry to schooling and work. It is extensively referenced, including papers published in 1997 and several lists of web sites, which will be of less interest outside America.

The medical chapters explain to a non-medical audience why a patient may have been prescribed a particular drug, but are of rather less help to a doctor seeking advice on how to manage a particular problem. Some of their practices may not be applicable in the United Kingdom: I think that few general practitioners would take on the primary responsibility for managing children with head injury just out of the intensive care unit, and paediatric psychopharmacologists, who

base their prescribing on SPECT or PET, may be hard to identify.

However the cognitive rehabilitation chapters are more valuable and emphasise ways to minimise any progressive deterioration in social skills and intellectual ability relative to the increasing abilities of the injured child's peers. Since the 1985 edition, it has become clear that retraining discrete cognitive tasks or teaching specific compensatory techniques does not lead to sustained or generalised improvement in functional ability, despite measurable improvements in neuropsychological tests. The authors' practice has now changed to encourage more generalised strategic thinking by the child, understanding their own limitations, and how to complete a task allowing for those limitations. Hence, instead of training with the decontextualised categorising and sequencing exercises which are often found in cognitive training programmes, they recommend meaningful text comprehension exercises, and production of organised narrative. This has also allowed a shift from intensive inpatient therapy to earlier discharge, with therapists now spending more time training families and school teachers to treat the child at home.

This book fills an important gap in the rehabilitation literature, but it is not an easy read: its 480 pages are filled with small print, hardly any figures, too many words, and far too few full stops.

STEPHEN KIRKER

**Subarachnoid Haemorrhage.** Edited by TAKEHIKO YANAGIHARA, DAVID G PEIPGRAS, and JOHN L D ATKINSON. (Pp 584, US\$195). Published by Marcel Dekker Inc, New York, ISBN 0-8247-9519-9.

This book is a synopsis of the current medical and surgical management of patients with subarachnoid haemorrhage. It represents a series on neurological disease and therapy, and has been compiled by 27 contributors who have been exposed to the Mayo Clinic experience over the past 30 years. The book consists of 18 chapters starting with pathophysiological and pharmacological concerns before considering the epidemiology, clinical presentation, investigations, and management. Each chapter is written from a personnel experience point of view, but is backed up by reference to the key literature on the subject. The chapter on the epidemiology of subarachnoid haemorrhage considers the difficulties in studying such patients paying address to selection bias and referral populations etc, and I found this particularly useful.

The Mayo Clinic is recognised for its surgical excellence of neurovascular conditions, and the authors have taken full advantage of their experience in the form of highly readable and understandable chapters. Various surgical approaches are supported by case illustrations, which include some of their own disasters. The book concludes with a chapter on the latest developments in interventional neuroradiology, and an important chapter on the rehabilitation after subarachnoid haemorrhage, a subject which is often missing in texts of this type.

In summary I found that this addition considering subarachnoid haemorrhage is a useful addition to the neurovascular bookcase. I would recommend it to those with a neurosurgical, neurological, or rehabilitative interest in neurovascular disorders.

PETER KIRKPATRICK